

Aromatase Inhibitor Pharmacogenomics Study

Mayo and Indiana PGRNs

Study Chairs

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Issues with AIs

- Some patients are intolerant of aromatase inhibitors
- About one in four women “suboptimally adherent” to anastrozole adjuvant therapy for early breast cancer (Partridge et al. J Clin Oncol, February 1, 2008)
- Some patients continue to have relapse of breast cancer despite AI therapy
- Does one dose fit all?

Mayo-MDA-MSKCC PGRN AI Pharmacogenomics Study

Hypothesis: Inherited variation in anastrozole PK and/or PD contributes to individual variation in anastrozole efficacy and/or side effects

Phenotypes: Hormone levels, drug and metabolite levels, bone density, breast density

Study Population: 1000 breast cancer patients from Mayo, MDA, MSKCC

Mayo-MDA-MSKCC PGRN AI Study

- **HPLC/MS analysis:** plasma anastrozole and anastrozole metabolites (Indiana University PGRN)
- **Plasma steroid hormone assays:** E1, E2, E1-conjugates, testosterone, androstenedione (Taylor Technology)

Mayo-MDA-MSKCC PGRN AI Study (cont.)

- **Bone mineral density:** prodigy device scanning forearm, hip and lumbar spine
- **Mammographic breast density:** percent density using Cumulus software
- **GWAS:** mid-2008

Eligibility

- Postmenopausal female (≥ 18 yrs) with resected breast cancer that was AJCC (6th edition) stage I, II, or III
- Tumor: ER and/or PgR positive
- Planned treatment with anastrozole, 1 mg per day
- Not allowed: prior use of any endocrine therapy within 6 months except tamoxifen

Mayo-MDA-MSKCC PGRN AI Study

Baseline: Questionnaire, hormone assays, DNA,
mammogram,
bone mineral density



Start anastrozole



4-24 weeks: Hormone assays,
blood drug levels



1 year: Blood draw, questionnaire
mammogram, bone mineral density

Patients for Whom Blood Sent for Hormones and Drug Levels

206: Blood sent

17: Excluded

13 Drug levels zero

3 On drug < 4 weeks

1 No hormone levels

189 patients analyzed

Patient Characteristics

Age, yrs, Med (range)	61 (39-82)
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BMI

Median

27.5

Range

17.7- 44.7

Prior Chemotherapy

Yes

40%

No

53%

Missing

6%

Prior Tamoxifen

Yes

11%

No

74%

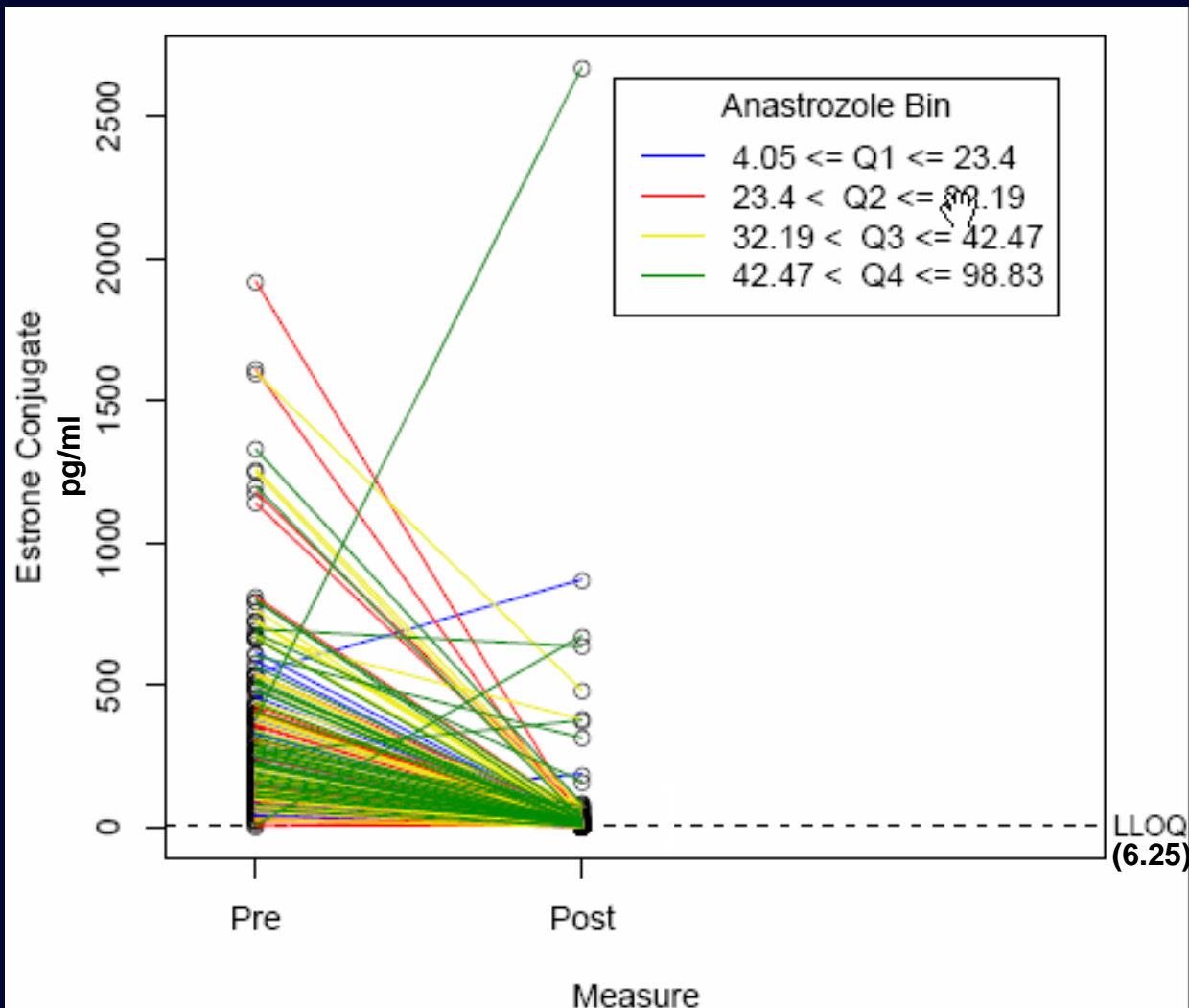
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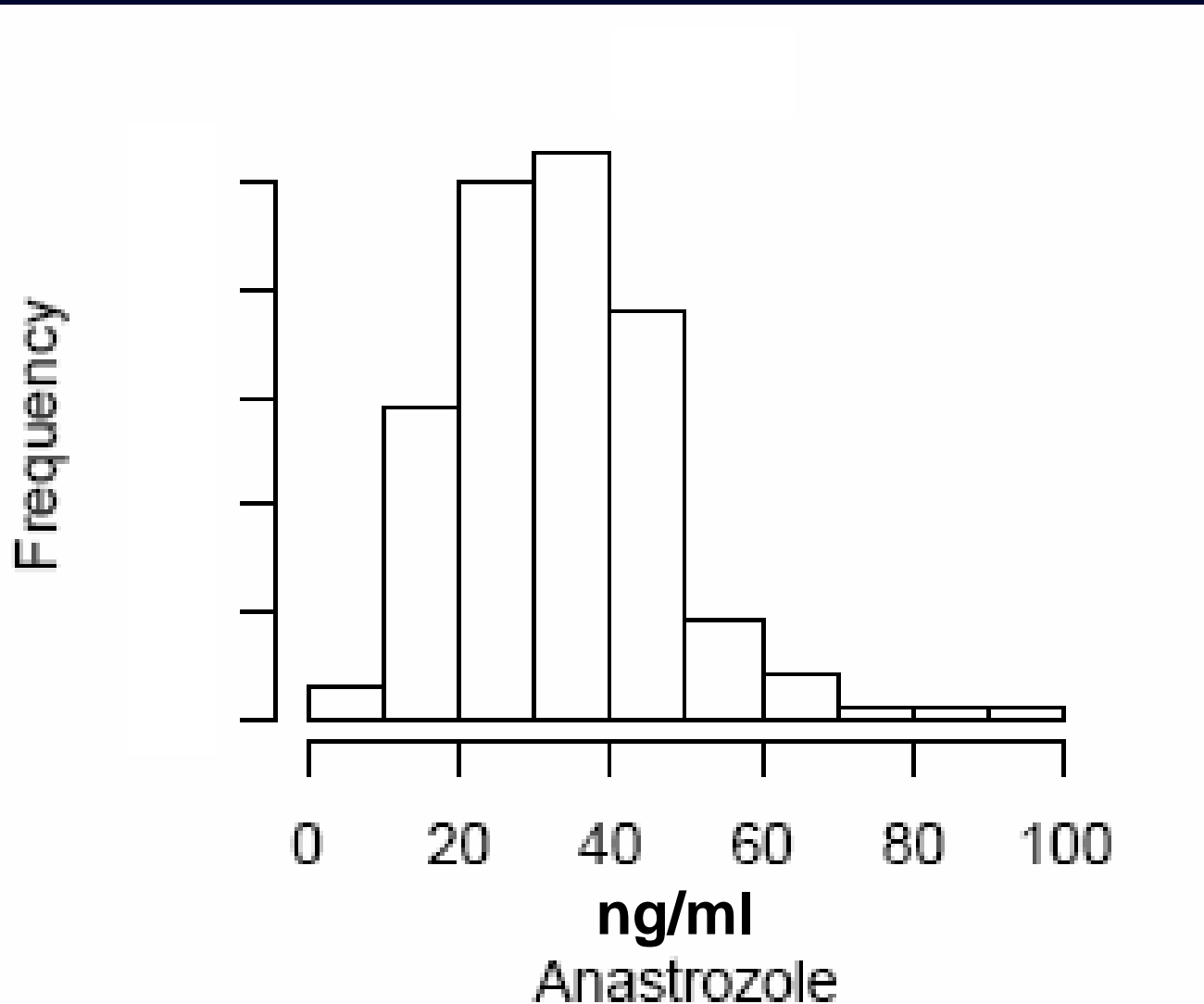
Estrone Conjugates

Pre and Post Anastrozole

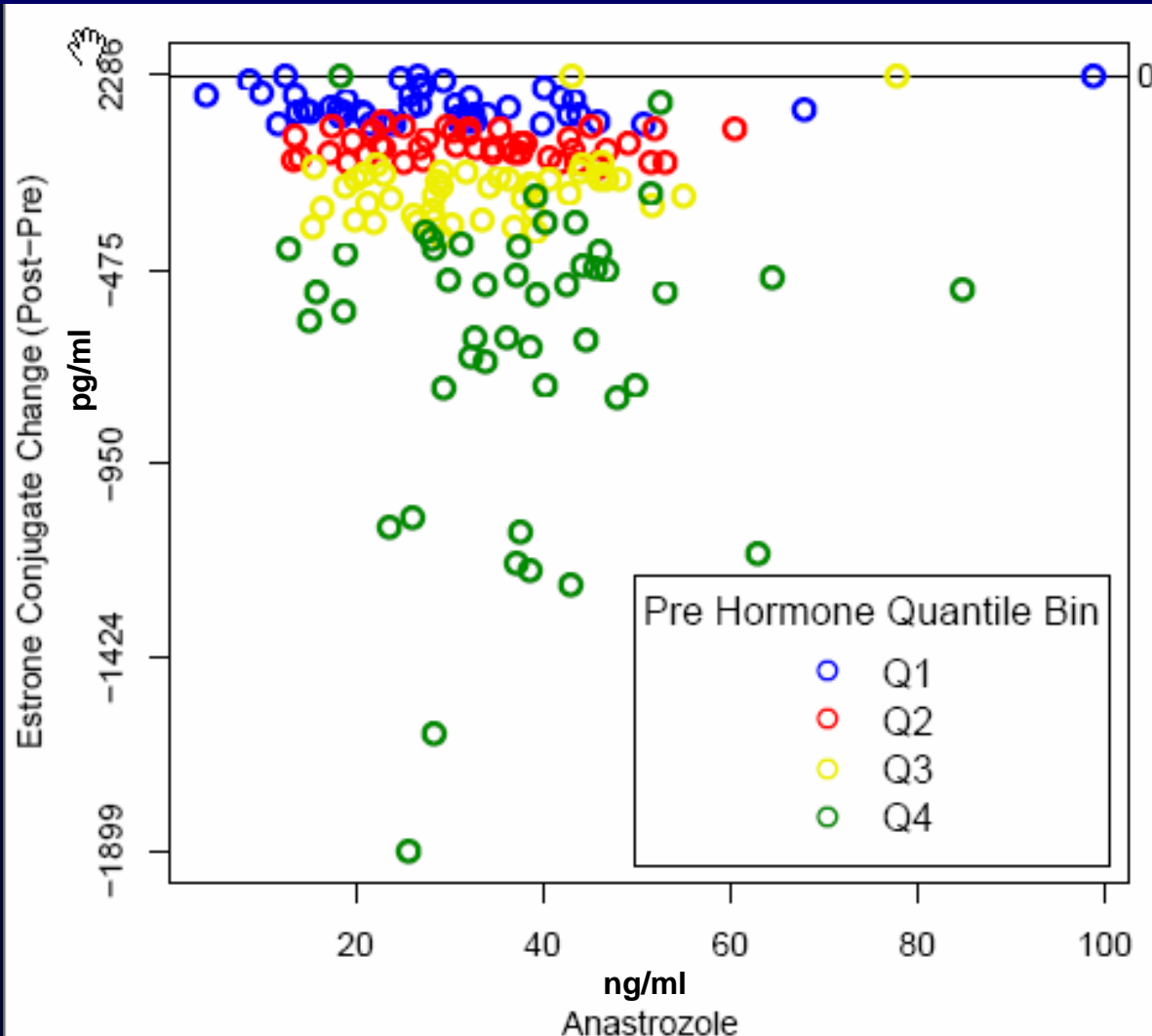
According to Quartile of Anastrozole



Frequency Distribution for Anastrozole Levels



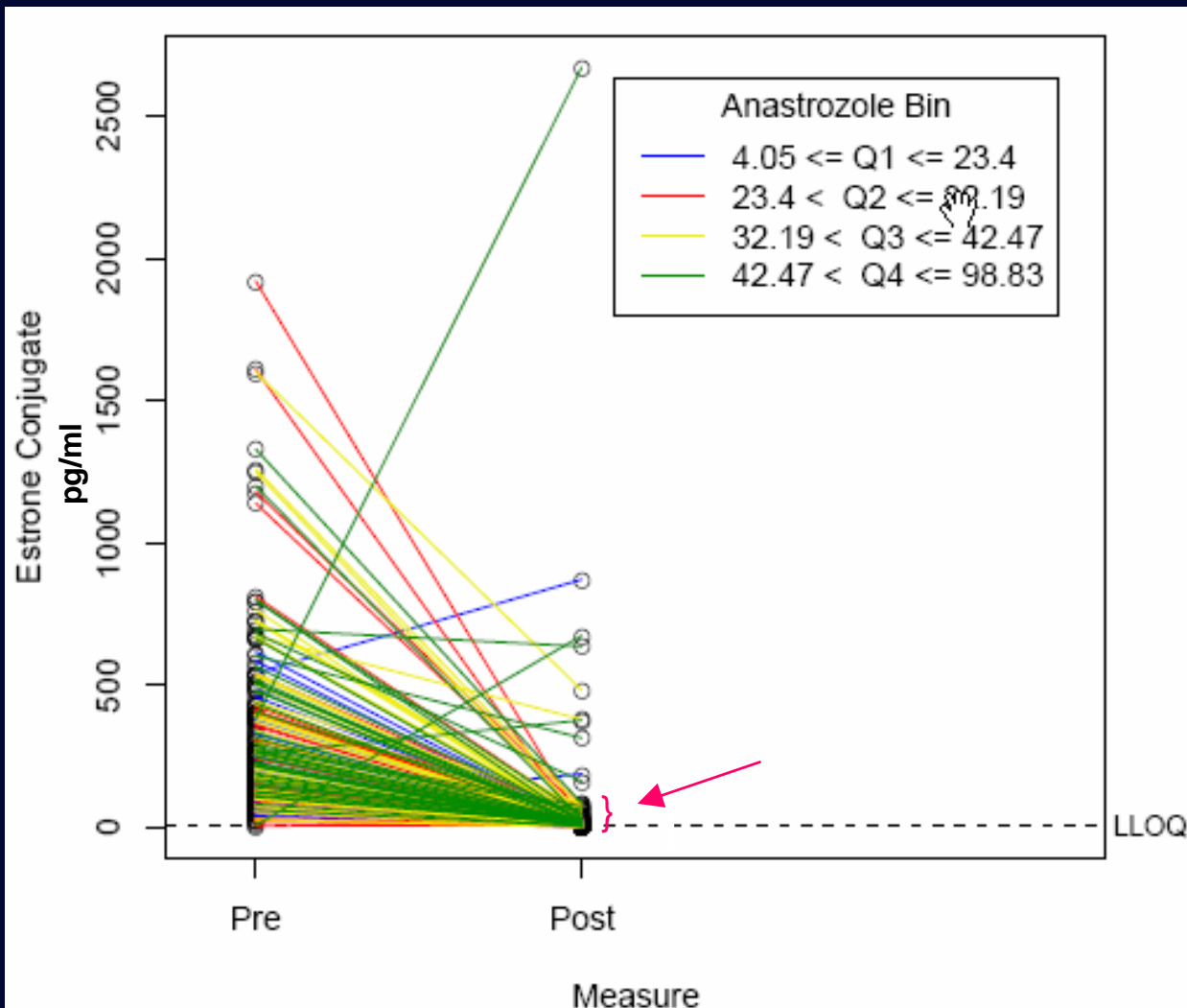
Change in Estrone Conjugate Level According to baseline Quartile Level and Anastrozole Level



Estrone Conjugates

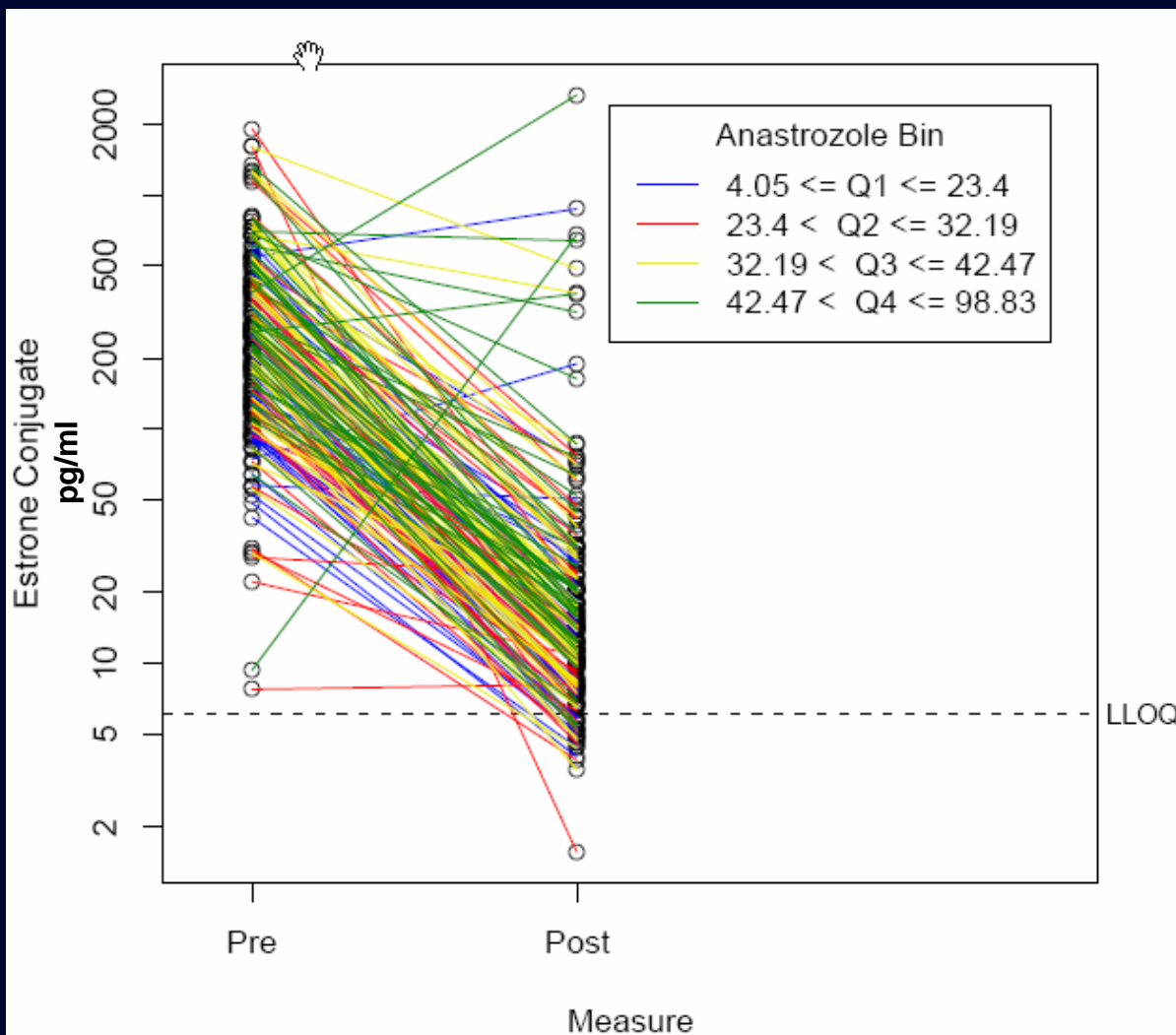
Pre and Post Anastrozole

According to Quartile of Anastrozole



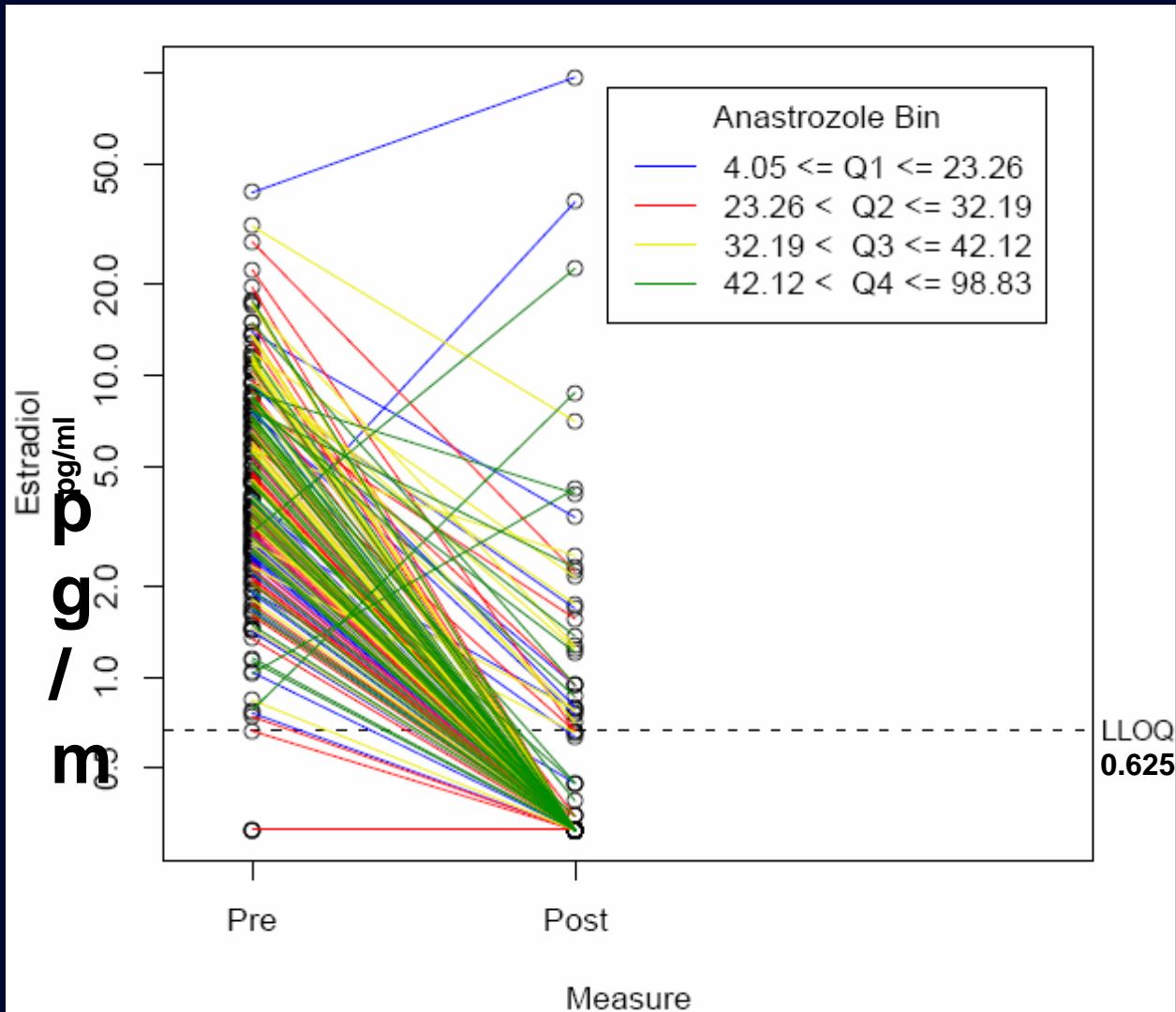
Estrone Conjugates Pre and Post Anastrozole According to Quartile of Anastrozole

Log
Scale



Estradiol Pre and Post Anastrozole According to Quartile of Anastrozole

Log
Scale



Conclusions

- Substantial variability in
 - levels of E1, E2, E1-conjugates
 - levels of androstenedione, testosterone (data not shown)
 - Parent drug levels
 - metabolites (data not shown)
- Substantial, 13/206 (6%) non-adherence in first several months
- Analysis is ongoing
- Will have data and GWAS on 600 pts by fall